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Systematic Review

Assessment of Serum VEGF Levels in Ovarian Cancer Prognosis: A Meta-Analysis

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Abstract

Background: This meta-analysis aimed to comprehensively assess the relationship between serum vascular endothelial growth factor (VEGF) levels and the prognosis of ovarian cancer. Recently, VEGF has been widely recognized as an important biomarker in tumorigenesis and development. Thus, this study aimed to clarify this association to provide evidence for clinical practice. **Methods**: A comprehensive literature search was conducted in PubMed, Wiley Library, Web of Science, Wanfang, VIP, and China National Knowledge Infrastructure (CNKI) databases from inception to June 30, 2024. A total of 2767 records were initially identified and screened; 9 studies met the inclusion criteria and were included in the meta-analysis. Data were analyzed using RevMan 5.3 and R 4.4.2 software. The quality of the included studies was assessed according to predetermined criteria. **Results**: This meta-analysis revealed that serum VEGF levels were significantly higher in ovarian cancer patients than in the normal control group (mean difference [MD] = 210.00; 95% confidence interval [CI]: 96.92–323.09). In addition, serum levels of VEGF were significantly higher in patients with advanced ovarian cancer compared with those with early-stage ovarian cancer (MD = –173.88, 95% CI: –290.28 to –57.49). Analysis of serum VEGF levels before and after surgical treatment showed a significant decrease after surgery (MD = 242.92, 95% CI: 154.66–331.17). Prognostic analysis showed a significant association between serum VEGF levels and overall survival (OS) (hazard ratio (HR) = 2.48, 95% CI: 1.84–3.34). However, the association with disease-free survival (DFS) was not statistically significant (HR = 1.29, 95% CI: 0.87–1.93). **Conclusion**: This meta-analysis demonstrates that elevated serum VEGF levels are associated with ovarian cancer progression and reduced overall survival. Although no significant association with DFS was found, serum VEGF levels remain a potential predictive biomarker worthy of further investigation. Future large-scale prospective studies are needed to confirm the clinical utility of serum VEGF in the management of ovarian cancer. **Registration**: The study has been registered on https://www.crd.york.ac.uk/prospero/ (registration number: CRD420251090777; registration link: https://www.crd.york.ac.uk/PROSPERO/view/CRD420251090777).

Keywords: VEGF; prognosis; survival analysis; meta-analysis

1. Introduction

Ovarian cancer is a malignancy with high incidence and mortality rates among gynecological tumors. Approximately 90% of clinically diagnosed ovarian cancers are epithelial tumors, which encompass various histological types [1]. These subtypes exhibit substantial differences in molecular alterations, clinical behavior, and treatment outcomes. The remaining 10% are non-epithelial ovarian cancers, primarily including germ cell tumors, sex cord-stromal tumors, and rare variants such as small cell carcinoma [1,2]. Among these, germ cell tumors are the most common ovarian malignancies in women under 30 years of age. About 60%–70% of patients are diagnosed at an early stage, with most cases presenting as unilateral lesions and generally demonstrating favorable prognosis [2]. Early symptoms are often inconspicuous, and effective screening tools for the general population are still lacking, leading to frequent diagnosis at an advanced stage [1]. This late-stage diagnosis contributes to more complex and costly treatments. This diagnostic challenge also has economic implications, as ovarian cancer remains the most expensive cancer to treat per patient. Considerable efforts have been invested over the past decade to evaluate cost-effective strategies for early detection and prevention. For instance, the average initial cost in the first year can amount to approximately USD 80,000, while costs in the final year of life may increase to USD 100,000 [3]. Globally, ovarian cancer affects 9.2 per 100,000 Asian women [4]. Owing to the lack of early warning indicators, over 70% of patients are diagnosed at an advanced stage and have a poor prognosis [4]. Despite continuous advancements in surgery, chemotherapy, and targeted therapy, the overall survival rate remains low. Germline Breast Cancer Gene 1/Breast Cancer Gene 2 (*BRCA1/2*) mutations, which are present in approximately 6%–15% of patients, are the most significant known genetic risk factors for epithelial ovarian cancer. Compared with non-carriers, *BRCA1/2* carriers tend to exhibit a better response to platinum-based chemotherapy. Although these patients are often diagnosed at a later stage

and with higher-grade histology, their enhanced chemosensitivity partially translates into improved survival outcomes [5]. The pathogenesis of ovarian cancer involves multiple factors, including aberrant signaling pathways, epigenetic alterations, and genetic mutations, which collectively drive tumor progression [6]. Among these, the Phosphoinositide 3-kinase (PI3K) pathway is frequently upregulated in epithelial ovarian cancer and has been shown to play an important role in chemoresistance and the maintenance of genomic stability. As PI3K is involved in key processes such as DNA replication and cell cycle regulation, its inhibition may Aurora kinase B activity, a spindle assembly checkpoint protein, leading to increased chromosomal lagging, genomic instability, and ultimately mitotic catastrophe [7]. Ovarian cancer is challenging to treat owing to the absence of early symptoms and effective prognostic markers, resulting in limited therapeutic efficacy and compounding clinical difficulties. Currently, Cancer Antigen 125 (CA125) and Human Epididymis Protein 4 (HE4) are the only approved serological biomarkers for epithelial ovarian cancer, but their insufficient sensitivity for early detection often leads to diagnosis at advanced stages [8]. To overcome the limitations of single-marker approaches, researchers have developed multivariate index assays (MVI), such as the Risk of Ovarian Malignancy Algorithm (ROMA), which incorporates menopausal status, CA125, and HE4 results in assess malignancy risk in patients with pelvic masses [8]. Emerging evidence suggests that miRNAs may hold significant potential for the prediction and diagnosis of epithelial ovarian cancer. However, their clinical application as biomarkers requires further investigation, particularly in standardizing sample processing protocols and improving detection platforms for miRNA quantification in both tumor tissues and blood [8]. The high degree of tumor heterogeneity further increases the complexity of diagnosis and individualized treatment, and more precise molecular markers are urgently needed to improve patient prognosis. Angiogenesis is a key mechanism for tumour growth and metastatic spread. Vascular endothelial growth factor (VEGF), which plays a key role in angiogenesis, is abundantly present in a variety of malignant tumours and is associated with tumour aggressiveness and poor prognosis [9].

VEGF is a key mediator of angiogenesis and plays a significant value in tumour growth and metastasis [10,11]. Its expression is elevated in a variety of solid tumours and is associated with poor prognosis [12,13]. In ovarian cancer, high expression of VEGF is closely associated with disease progression and may serve as an important biomarker reflecting tumor burden. Maryam *et al*. [14] noted that serum VEGF-A could serve as an early diagnostic marker for ovarian cancer, with the potential to outperform the traditional biomarker CA125. In addition, Yang and Cao [15] emphasized the impact of VEGF in cancer metastasis and systemic diseases, further supporting its potential application as a diagnostic and prognostic indicator of ovarian cancer.

Ding *et al*. [16] reported that serum VEGF-C levels were correlated with the response to bevacizumab maintenance therapy in patients with primary ovarian cancer, suggesting that VEGF expression levels may influence therapeutic sensitivity. In addition, Mishra *et al*. [17] explored the relationship between VEGF and novel antitumor therapies, emphasizing the role of VEGF as a potential target in ovarian cancer treatment. However, the specific mechanisms by which VEGF expression levels affect ovarian cancer progression and treatment response require further elucidation. Therefore, systematically exploring the role of VEGF in ovarian cancer, especially in terms of its application as a biomarker and therapeutic target, is an important direction for future research.

Although several meta-analyses have evaluated the use of VEGF in ovarian cancer prognosis, further systematic studies are still urgently needed in this area. Yu *et al*. [18] pointed out that VEGF acts as a prognostic biomarker, but there are limitations such as insufficient sample size and selection bias in the study. Trifanescu *et al*. [19] emphasized the correlation between VEGF and oxidative stress markers, suggesting that the role of VEGF may be affected by other biomarkers, and thus a multifactorial approach is needed to clarify its prognostic significance. Guo and Lu [20] demonstrated the prognostic significance of high VEGF expression in ovarian cancer, but the generalizability of their findings may be limited by the diversity of the study population. The analysis of circulating VEGF as a diagnostic marker for ovarian cancer by Liang *et al*. [21], although revealing its potential value, lacked a careful analysis of patients with different subtypes. To address these limitations, this meta-analysis aims to rigorously evaluate the prognostic role of serum VEGF levels in ovarian cancer by employing stricter inclusion criteria and a comprehensive analytical approach.

2. Methods

2.1 Literature Search Strategy

We systematically searched the English databases (PubMed, Wiley Library, Web of Science) and the Chinese databases (Wanfang, VIP, and CNKI) from inception to June 30, 2024. This study was registered with PROSPERO (CRD420251090777) and followed PRISMA guidelines. The search strategy was based on four key concepts: (1) ovarian cancer, (2) prognosis, (3) VEGF, and (4) serum/blood. The full, detailed search strings for each database are provided in **Supplementary File 1**.

2.2 Search Limitations

The search encompassed records from the inception of each database until June 30, 2024, and was restricted to publications in Chinese and English.

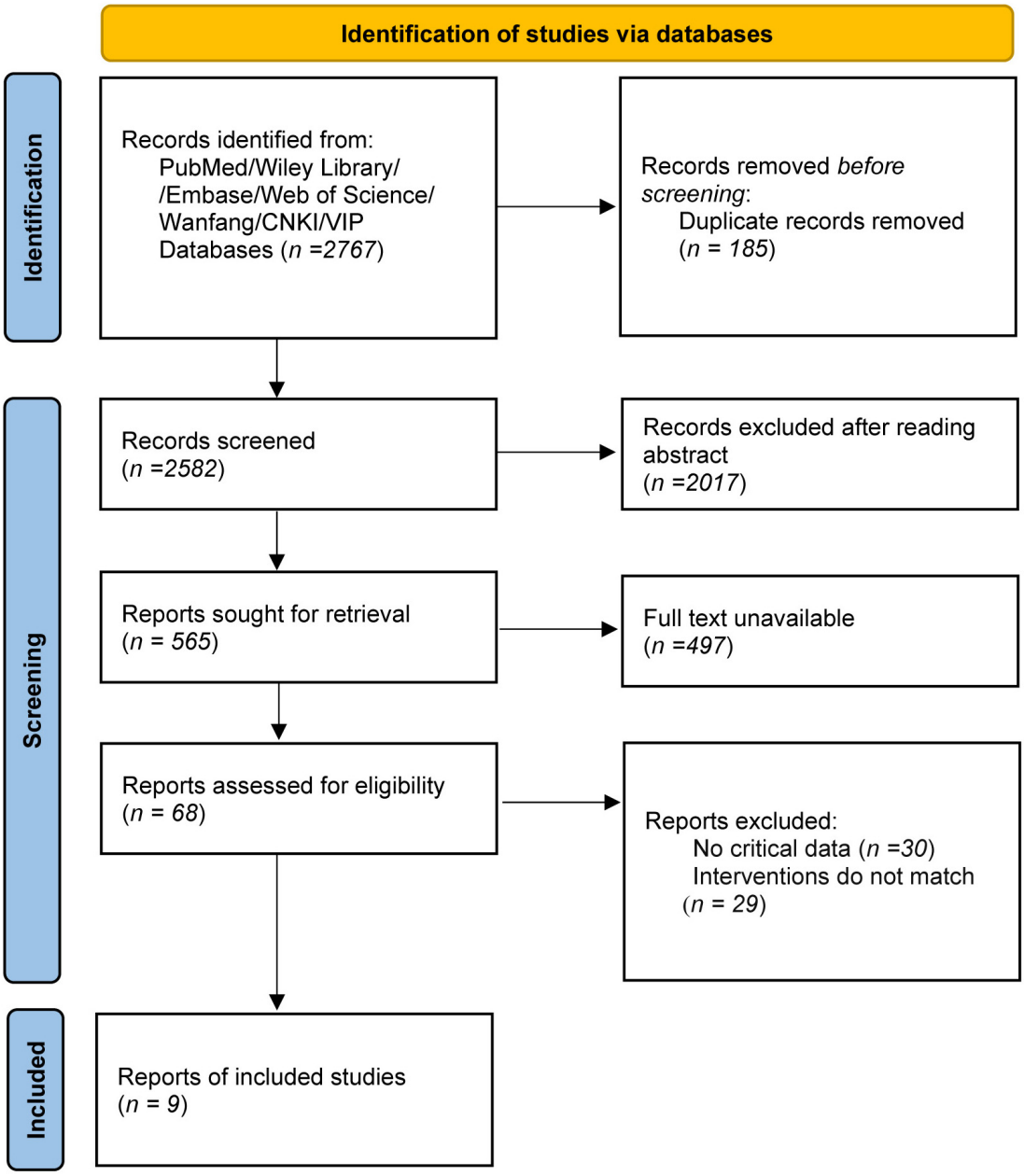

Fig. 1. Literature screening flowchart.

2.3 Inclusion and Exclusion Criteria

2.3.1 Inclusion Criteria

(1) Studies investigating the correlation between serum VEGF levels and prognosis of ovarian cancer; (2) Studies reporting relevant clinicopathological factors (e.g., patient age, ovarian cancer stage and prognosis); (3) Literature containing sufficient data to calculate Hazard Ratios (HRs) and their 95% confidence intervals (CIs); (4) Studies that measured serum VEGF levels using enzyme-linked immunosorbent assay (ELISA); (5) Studies with a minimum sample size of 30 patients; and (6) Prospective or retrospective cohort studies.

2.3.2 Exclusion Criteria

(1) Studies with incomplete or inaccurate raw data; (2) Previously published meta-analyses, or original studies that had been included in earlier meta-analyses; (3) Studies that did not meet the criteria for inclusion in the analyses; (4) Categories consisting only of abstracts, letters, editorials, expert opinions, or case reports; (5) Reviews, and non-human or *in vitro* studies.

2.4 Data Extraction

We screened the titles and abstracts of the retrieved articles and manually eliminated irrelevant studies. After a thorough examination of the available literature, we screened abstracts to identify relevant studies and to exclu-

Table 1. Basic characteristics of included studies.

Author and year	Sample size		Age		Study design	Outcome indicators	Follow-up time	Primary treatment regimen
	Ovarian cancer	Healthy control	Ovarian cancer	Healthy control				
Sallinen *et al*., 2014 [22]	132	32	59 [26–83]	60 [36–81]	Prospective	①②	5 years	Platinum-based chemotherapy
Dobrzycka *et al*., 2015 [23]	92	94	56 [32–76]	54.7 [21–72]	Retrospective	①③⑤	5 years	Platinum-based chemotherapy
Li *et al*., 2004 [24]	120	90	51.7 [31–76]	37.6 [23–52]	Prospective	①④⑤	1 year	Platinum-based chemotherapy + Comprehensive staging surgery
Masoumi-Moghaddam *et al*., 2015 [25]	100	-	62 [35–84]	-	Retrospective	①③	8 years	Platinum-based chemotherapy
Li *et al*., 2004 [26]	61	11	54.38 [40–78]	49.2 [43–67]	Retrospective	⑤	2 years	Platinum-based chemotherapy + Cytoreductive surgery
Zhang *et al*., 2024 [27]	100	-	55.01 ± 8.49	-	Retrospective	①	2 years	Platinum-based chemotherapy + Comprehensive staging surgery
Ma *et al*., 2021 [28]	106	122	55 [45–64]	32 [26–41]	Retrospective	④⑤	Not Reported	Platinum-based chemotherapy + Comprehensive staging surgery
Tan *et al*., 2000 [29]	76	10	55 [33–73]	38 [24–52]	Retrospective	⑤	3 years	Comprehensive staging surgery + Postoperative chemotherapy
Luo *et al*., 2017 [30]	42	42	46.5 ± 12.3	47.2 ± 12.6	Retrospective	④	3 5 years	Comprehensive staging surgery + Postoperative chemotherapy + Debulking surgery

Note: ① Overall survival (OS), ② Recurrence-free survival, ③ Disease-free survival (DFS), ④ Pre- and post-operative vascular endothelial growth factor (VEGF) levels, ⑤ Ovarian cancer stage.

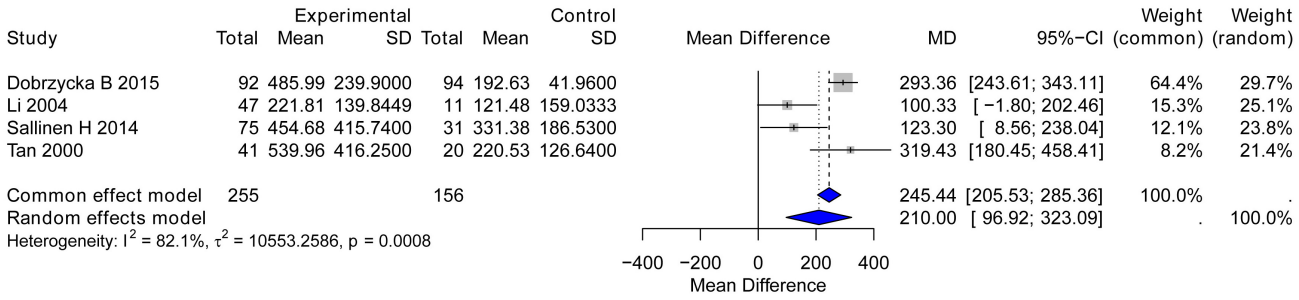

Fig. 2. Forest plot of VEGF levels between the two groups. VEGF, vascular endothelial growth factor.

de any duplicates. The full text of each potentially eligible article was reviewed to determine its applicability. Any disagreements during the study selection process were resolved through consensus or by consulting a third reviewer. The final dataset of the study included key information such as first author, year of publication, age, sample size, study type, outcome metrics, and duration of follow-up.

2.5 Main Observational Indicators

The outcome measures included: (1) the difference in serum VEGF levels between the healthy control group and patients with ovarian cancer; (2) differences in serum VEGF levels between patients with different stages of ovarian cancer; (3) the change in serum VEGF levels from preoperative to postoperative period in patients with ovarian cancer; (4) overall survival (OS); and (5) disease-free survival (DFS).

Indicator Measurement Methods: For the measurement of serum VEGF levels, included studies were required to measure serum VEGF levels by ELISA. For measures of overall survival and disease-free survival, studies were asked to provide clear definitions of follow-up time and outcomes for survival analysis.

2.6 Literature Quality Assessment

This study employed the Newcastle-Ottawa Scale (NOS) to evaluate the quality of all included studies. The scale comprises three domains: subject selection, comparability between groups, and outcome assessment, with a total of eight items. For the "subject selection" and "outcome assessment" domains, one star can be awarded for each satisfied criterion. In the "comparability" domain, a maximum of two stars can be allocated. The total score for each study ranges from 0 to 9, with 9 being the highest possible score. Studies with a score of <6 were considered low quality, whereas those with a score of ≥ 6 were considered high quality.

2.7 Statistical Methods

In this study, statistical analyses were performed using Review Manager (RevMan) software (version 5.3, The Cochrane Collaboration, London, UK) and R software (version 4.4.2, R Core Team, R Foundation for Statistical Computing, Vienna, Austria) for meta-analysis. Heterogeneity was assessed using the I^2 statistic. An I^2 value $\leq 50\%$ indicated low heterogeneity, and a fixed-effects model was applied; an I^2 value $> 50\%$ indicated substantial heterogeneity, and a random-effects model was employed. Additionally, Egger's test was conducted to evaluate publication bias. Pooled analyses were performed using the mean difference (MD) and its 95% confidence interval (CI) for continuous variables, and the hazard ratio (HR) and its 95% CI for survival data. A p value < 0.05 were considered statistically significant. All statistical analyses were performed in strict accordance with the recommendations of the Cochrane Collaboration Network to ensure the scientific validity and credibility of the results.

3. Results

3.1 Literature Search Results

A total of 2767 records were retrieved (1725 in English and 1042 in Chinese). After screening titles and abstracts, 565 records remained. Sixty-eight full-text articles were retrieved for full-text review against the inclusion and exclusion criteria. Finally, 9 studies that met the inclusion criteria were included, as shown in Fig. 1.

3.2 Characteristics of Included Literature and Evaluation of Literature Quality

A total of 9 studies were included in this meta-analysis, involving a total of 1230 patients, including 829 ovarian cancer patients and 401 healthy controls, as shown in Table 1 (Ref. [22–30]).

According to the quality assessment results based on the NOS scale, four studies scored 8 points, three scored 7 points, and two scored 6 points. The primary factor contributing to the score reduction was relatively low follow-up completeness, as detailed in Table 2 (Ref. [22–30]).

3.3 Meta-Analysis Results

3.3.1 VEGF Levels in Healthy Control and Ovarian Cancer Groups

In this study, the serum VEGF levels of the healthy control group and the ovarian cancer group were comparatively analysed. Patients in the ovarian cancer group had significantly higher serum VEGF levels than those in

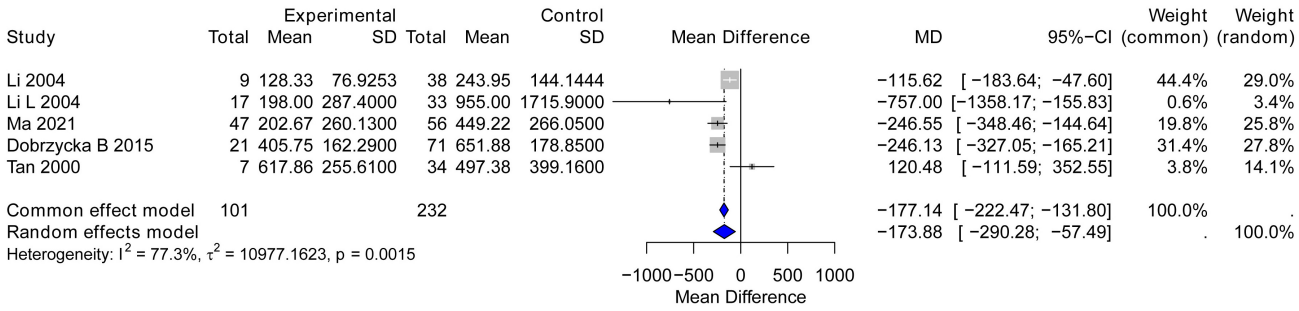

Fig. 3. Forest plot of VEGF levels in different stages of ovarian cancer.

Table 2. Quality assessment of included studies using NOS.

Study authors and publication year	Selection of cases			Comparability		Outcome assessment			Score
	1	2	3	4	5	6	7	8	
Sallinen *et al*., 2014 [22]	★	★	★	★	★	★	★	★	8
Dobrzycka *et al*., 2015 [23]	★	★	★	★	★	★	★		7
Li *et al*., 2004 [24]	★	★	★	★	★	★	★	★	8
Masoumi-Moghaddam *et al*., 2015 [25]	★	★	★	★		★	★	★	7
Li *et al*., 2004 [26]	★	★	★	★	★	★	★	★	8
Zhang *et al*., 2024 [27]	★	★			★	★	★	★	6
Ma *et al*., 2021 [28]	★	★	★	★	★	★			6
Tan *et al*., 2000 [29]	★	★	★	★	★	★	★		7
Luo *et al*., 2017 [30]	★	★	★	★	★	★	★	★	8

Note: 1. Appropriateness of case definition and diagnosis; 2. Representativeness of cases; 3. Selection of controls; 4. Ascertainment of controls; 5. Comparability between groups; 6. Outcome measurement methods; 7. Sufficiency of follow-up duration; 8. Completeness of follow-up. NOS, Newcastle-Ottawa Scale. Each star (★) indicates that the study met the criterion for that specific NOS item and was awarded one point.

the healthy control group (MD = 210.00, 95% CI: 96.92–323.09), as shown in Fig. 2.

3.3.2 VEGF Levels in Different Stages of Ovarian Cancer

In this study, we compared serum VEGF levels in ovarian cancer patients with different stages. Patients with advanced ovarian cancer had significantly higher VEGF levels than those with early-stage disease (MD = –173.88, 95% CI: –290.28 to –57.49). This finding suggests that serum VEGF levels gradually increase with disease progression, possibly reflecting increased tumour neovascularisation as well as increased tumour burden, as shown in Fig. 3.

3.3.3 VEGF Levels Before and After Surgery for Ovarian Cancer

A pooled analysis of three studies reporting perioperative serum VEGF levels showed a significant decrease following surgery (MD = 242.92, 95% CI: 154.66–331.17), as shown in Fig. 4.

3.3.4 Overall Survival (OS)

Five studies assessed the association between serum VEGF levels and OS. No significant heterogeneity was observed (p = 0.48, I^2 = 0%), and a fixed-effects model was used. The pooled analysis demonstrated a significant association between higher serum VEGF levels and worse overall survival (HR = 2.48, 95% CI: 1.84–3.34), as shown in Fig. 5.

3.3.5 Disease-Free Survival (DFS)

In this study, 2 articles clearly illustrated the relationship between serum VEGF levels and DFS. The results showed that the correlation between serum VEGF levels and DFS did not reach statistical significance (HR = 1.29, 95% CI: 0.87–1.93). As shown in Fig. 6.

3.3.6 Publication Bias

Publication bias was assessed statistically using Egger's test, as the inclusion of fewer than 10 studies per outcome rendered funnel plots unreliable. As fewer than 10 studies were included to assess publication bias, Egger's test was employed to evaluate all incorporated indicators. The results indicated that for the study examining serum VEGF levels and OS, the Egger's test yielded a p-value of 0.1892 > 0.05, suggesting no significant publication bias.

4. Discussion

The main findings of this meta-analysis indicate that serum VEGF levels are significantly elevated in patients

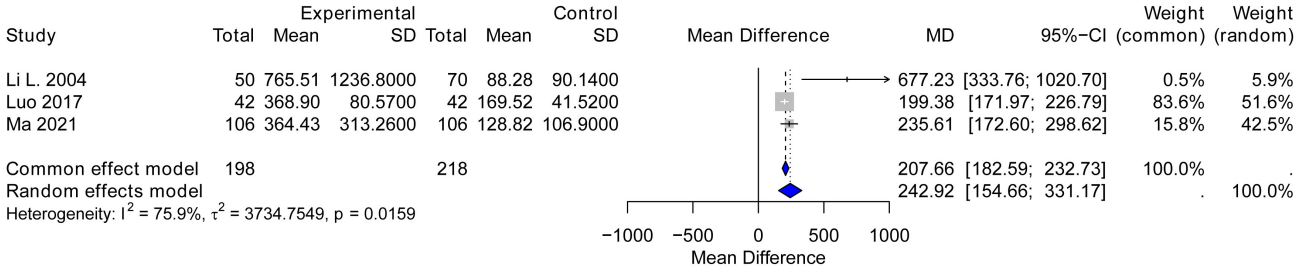

Fig. 4. Forest plot of VEGF levels before and after surgery for ovarian cancer.

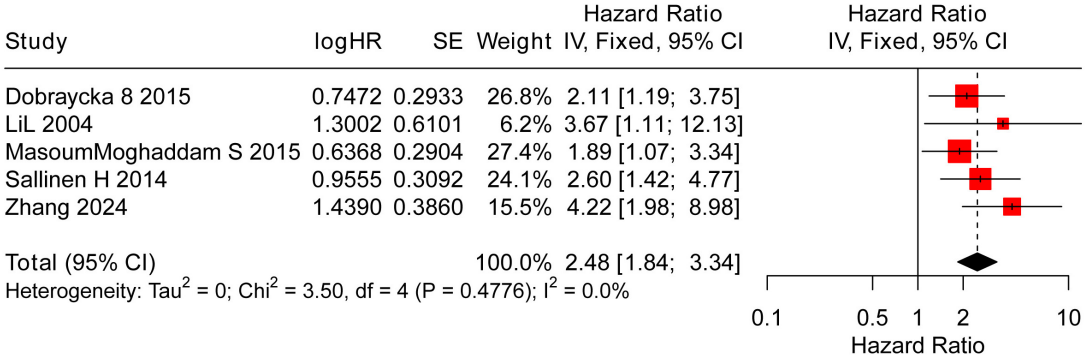

Fig. 5. Forest plot of overall survival.

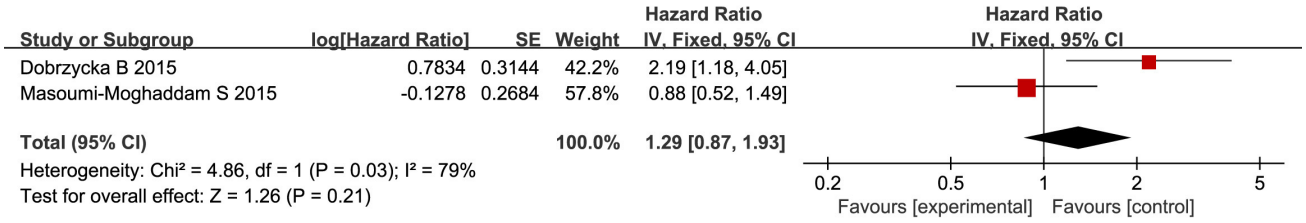

Fig. 6. Forest plot of disease-free survival.

with ovarian cancer and are positively associated with disease progression and reduced overall survival. Although VEGF levels decreased after surgery, the association with disease-free survival was not significant, suggesting the complexity of VEGF in ovarian cancer prognosis. These results highlight VEGF as a potential biomarker for clinical practice and emphasize its value in ovarian cancer management. Therefore, further exploration of the clinical significance and mechanism of VEGF as a prognostic marker for ovarian cancer is essential, especially in the context of the current lack of effective early screening tools. Studies have shown [31,32] that VEGF is not only associated with tumor growth and metastasis, but may also be influenced by other biomarkers, which provides a direction for future multifactorial studies.

Ovarian cancer is a common malignant tumour of the female reproductive system that is often overlooked in its early stages, and women of all ages can develop this disease, but postmenopausal women are at a higher risk [33]. Recent studies have further revealed that epithelial ovarian cancer can be broadly categorized into two types: Type I and Type II [34]. Type I tumors typically exhibit slow growth, are genetically stable, and often originate from recognizable precancerous lesions such as endometriosis or borderline tumors of low malignant potential. In contrast, Type II tumors demonstrate aggressive behavior from the outset, with a tendency for early metastasis. High-grade serous carcinoma, the most common subtype of epithelial ovarian cancer accounting for approximately 75% of all cases, primarily follows the Type II pathway and is frequently associated with mutations in the *p53* and *BRCA* genes [34]. In the absence of initial symptoms, a significant number of women are diagnosed at a late stage, thus complicating the treatment process [35]. It is noteworthy that in recent years, proteomic technologies such as mass spectrometry and protein microarrays have provided powerful tools for elucidating the underlying molecular signaling pathways and proteomic characteristics of ovarian cancer. Dynamic proteomic analysis of ovarian cancer and its response to treatment facilitates the identification of novel therapeutic targets, thereby reducing the occurrence of drug resistance and offering new strategies for improving patient prognosis [36]. Symptoms

may include bloating or abdominal pressure, dyspepsia, decreased desire to eat, pelvic discomfort, urinary frequency or urgency [35].

VEGF is a highly specific pro-angiogenic factor that promotes angiogenesis, endothelial cell migration, and proliferation by binding to appropriate receptors [37]. VEGF is involved in a variety of physiological functions such as those related to the female reproductive system, wound healing and embryonic development [38]. However, in cancer, VEGF expression is closely associated with ovarian cancer. Tiper *et al*. [39] demonstrated that VEGF levels were higher in ovarian cancer cultures by examining the levels of VEGF in cells and that the levels of VEGF were directly correlated with the disease condition. Therefore, targeting VEGF is an important strategy for ovarian cancer treatment.

Our meta-analysis showed that serum VEGF levels were significantly higher in patients with advanced ovarian cancer than in those with early-stage disease. Sen *et al*. [40] determined serum levels of VEGF, leptin etc. in patients with ovarian cancer attending the clinic between 2009 and 2011 as compared to healthy controls by using serum levels of VEGF in order to predict the malignancy of adnexal masses. The results of the meta-analysis showed that the serum levels of VEGF were significantly higher in patients with advanced ovarian cancer compared to patients with early ovarian cancer. Cooper *et al*. [41] confirmed significantly elevated serum VEGF levels in ovarian cancer, which were strongly associated with advanced disease features like ascites. Critically, their multivariate analysis established a high VEGF level (>380 pg/mL) as an independent predictor of poor survival (HR = 2.33), directly linking it to disease progression and prognosis. Taken together, evidence from both associative and prognostic studies strongly indicates that monitoring changes in VEGF levels can provide valuable information about the severity and progression of ovarian cancer.

Meta-analysis summarised three articles on VEGF levels before and after surgery. The significant decrease in VEGF levels following surgical intervention suggests successful tumour reduction. Postoperative monitoring of serum VEGF levels can provide a reference for evaluating surgical outcomes and patient prognosis. Hefler *et al*. [42] demonstrated that measurement of VEGF levels in the serum of patients with ovarian cancer prior to surgery can be a useful prognostic indicator. Notably, persistently high VEGF levels after surgery may indicate residual disease or an increased risk of recurrence. Regular testing of VEGF levels after surgery is essential to determine the efficacy of treatment and to predict the likelihood of recurrence.

Prognostic analyses showed a significant association between serum VEGF levels and OS, consistent with findings in other cancer types. Guo and Lu [20] histologically analyzed the prognostic significance of VEGF expression in ovarian cancer, which is consistent with our results. Shen *et al*. [43] also paid special attention to the expression of Phosphatase and Tensin Homolog (*PTEN*), Hypoxia-Inducible Factor 1-alpha (*HIF-1*α) and VEGF and the prognosis of ovarian cancer. The correlation between specific pathological features and prognosis was investigated in order to gain a deeper understanding of their impact on outcome.

In the clinical guidelines for serous ovarian cancer established by National Comprehensive Cancer Network (NCCN) and other organizations, the combination of platinum-based drugs, paclitaxel, and anti-vascular endothelial growth factor receptor antibodies (bevacizumab) is recommended as a second-line or later treatment option. Thus, anti-angiogenic therapy targeting the VEGF pathway (e.g., bevacizumab) has an established role in the treatment of serous ovarian cancer. However, recent studies [44] have shown that in ovarian cancer, bevacizumab may reduce disease progression for approximately one year after treatment initiation, but in the serous subtype, discontinuation of bevacizumab may increase subsequent disease progression regardless of Homologous Recombination Deficiency (HRD) status. Clinical research findings [45] suggest that bevacizumab may be more beneficial in first-line treatment.

The results of this meta-analysis indicate that serum levels of VEGF are significantly elevated in ovarian cancer patients and are associated with disease progression and reduced survival. This study highlights that, although the relationship between serum VEGF and DFS did not show statistical significance, its potential as a predictive biomarker for ovarian cancer warrants further investigation. DFS can be affected by a variety of factors, including treatment regimen, individual patient differences, and duration of follow-up. These factors, along with tumour characteristics, represent potential confounding variables for DFS. The patient's age, gender, underlying health status, and genetic background may all influence the development and prognosis of the disease. For example, different individuals have differences in immune system function and may have different resistance to tumor growth and spread. Some patients may have specific genetic variants that make them differently susceptible to tumors or responsive to treatment than other patients. These individual differences may interfere with the potential association between VEGF and DFS, making it difficult to observe a clear statistical relationship in the overall study. A shorter follow-up period may fail to adequately capture disease recurrence or progression, diluting the potential association between VEGF levels and long-term recurrence risk. This results in insufficient statistical power to draw significant conclusions, thereby underestimating the actual disease-free survival of patients. Longer follow-up times may be affected by more confounding factors, such as patients who may develop new health problems or receive other treatments during the follow-up period, which may interfere with the determination of the relationship between VEGF and DFS. Although all enrolled patients received platinum-based chemother-

apy, the completeness of cytoreductive surgery and the specific chemotherapeutic agents used were inconsistently reported across studies. These potent treatment interventions themselves have a decisive impact on DFS, which may far exceed the prognostic effect of baseline serum VEGF levels and thereby obscure the association of VEGF with DFS. Furthermore, tumour biology and VEGF expression and function may evolve over time, further complicating the assessment of their relationship with DFS. However, the influence of other adjuvant molecular markers or cytokines on DFS may be substantial, suggesting that VEGF alone may not be a primary determinant of this outcome.

Limitations

Despite comparing different aspects of VEGF levels and obtaining statistically significant results, this study has several limitations. This study incorporated multiple observational studies. Although a rigorous quality assessment was conducted, significant heterogeneity was observed across the studies. This heterogeneity may stem from differences in patient populations, including age, comorbidities, and hormone levels. Furthermore, there is currently a lack of standardized protocols for measuring VEGF levels, which may lead to variations in clinical applications across different medical institutions and affect the comparability of results. Future research should strive to establish uniform standards to minimize the impact of heterogeneity on the conclusions. Differences in methods and technical standards for the determination of VEGF levels in existing studies also pose challenges to the reliability and reproducibility of results. Different studies have employed various VEGF detection methods (such as ELISA and immunohistochemistry), which may vary in sensitivity and specificity, thereby affecting the consistency of VEGF level measurements. Therefore, future research should strive to adopt unified and standardized detection methods to ensure data comparability and accuracy. Owing to the small sample size and limited geographic diversity of the including studies, the generalizability of our findings to broader populations may be limited. To improve the reliability and representativeness of the results, future investigations should consider increasing the sample size and incorporating a wider range of regions and demographics. Although we assessed publication bias and using Egger's test, the limited number of included studies increases the risk of such bias, as small-sample studies are more likely to report positive results. Future research should aim to incorporate grey literature to mitigate this risk. Furthermore, since the original studies did not comprehensively report baseline patient characteristics and other relevant information, potential heterogeneity may have been introduced. Future studies should aim to report research data in a more standardized and comprehensive manner. In addition, future studies should investigate the effects of VEGF on ovarian cancer cell proliferation, apoptosis, invasion and metastasis, as well as its interactions with cellular and molecular components within the tumour microenvironment. The sample size should be enlarged to improve the statistical validity of the study, so as to more accurately evaluate the relationship between VEGF and the prognosis of ovarian cancer, and at the same time to increase the representativeness of the study to cover more patients with different types and stages of ovarian cancer; more types of ovarian cancers should be included, such as germ cell tumors and interstitial tumors of the sex cord, so as to explore the differences in the roles of VEGF in different types of ovarian cancers; and for the clinical application, the combination of VEGF and other biomarkers can provide a more accurate basis for the early diagnosis of ovarian cancer. In terms of clinical application, the combination of VEGF and other biomarkers can provide a more accurate basis for the early diagnosis of ovarian cancer, and the dynamic monitoring of VEGF levels can help to evaluate the disease progression and treatment effects. In conclusion, further research is warranted to better elucidate the role of VEGF in ovarian cancer, translate these findings into clinical practice, and ultimately improve patient outcomes.

5. Conclusion

The findings of this meta-analysis indicate that serum vascular endothelial growth factor levels are significantly elevated in patients with ovarian cancer and are associated with disease progression and reduced survival. Although the relationship between serum VEGF and disease-free survival was not statistically significant, its potential as a predictive biomarker for ovarian cancer warrants further investigation. Future studies should prioritize larger prospective trials to better establish the clinical relevance of vascular endothelial growth factor in ovarian cancer management.

Availability of Data and Materials

All data analyzed during the current meta-analysis study were extracted from previously published scientific articles which are cited and listed in the reference section of this manuscript. Therefore, no new primary data were generated, and the underlying data necessary to reproduce our findings are fully available within the cited references.

Author Contributions

LZ conceived and designed the study. LZ and SW developed the methodology. SW was responsible for software and formal analysis. DL performed validation and investigation. All authors contributed to the acquisition of resources. DL and SW curated the data. SW wrote the original draft. All authors contributed to reviewing and editing the manuscript. LZ supervised and administered the project. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG44541.

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